An estimated 5–10% of the total population is affected by chronic renal disease, which is considered a major cardiovascular risk factor. Diseases of civilization such as arterial hypertension, obesity, old age and diabetes are the most common prime risk factors for developing focal and segmental glomerulosclerosis (FSGS) and subsequent progressive loss of renal function. Many of the affected patients are unaware of their condition, so that the first manifestation of the renal disease epidemic is often cardiovascular events such as stroke or myocardial infarction. There is still no specific therapy available to treat FSGS. The major reason is that the exact pathogenesis of FSGS is incompletely resolved. However, in recent years major advances have been made, some of which will be highlighted here.

It is now generally accepted that a significant injury or loss of podocytes alone may trigger FSGS. This has been shown by partial ablation of podocytes in experimental animal models. Using a transgenic approach, different toxins could be targeted specifically to podocytes without injuring any other renal cells [1, 2]. Certainly, this does not exclude that also other yet unidentified factors may also trigger FSGS. Finally, it could be shown that glomerulosclerosis on its own shows a tendency to progress even though the initial triggering insult was no longer active or present [3].

It has also become clear that parietal epithelial cells (PECs) are involved in the pathogenesis of glomerulosclerotic lesions. While several earlier studies using immuno stainings for markers already suggested the presence of PECs in sclerotic lesions, definitive experimental proof was provided in a genetic cell fate tracking experiment [4]. However, it still remains to be shown whether PECs are present in all glomerulosclerotic lesions independent of the primary disease or injury.

In recent years, an academic discussion has emerged about how to interpret the functional role of PECs with regard to podocytopenia and glomerulosclerosis. Two alternative interpretations exist: PECs may function as an intrinsic progenitor population or PECs may become activated and invade and destroy segments of the glomerular tuft via adhesion (reviewed in [5]). This editorial comment will focus on recent developments regarding the first interpretation.

In 2009, it was proposed by the group of Romagnani and us that PECs may function in replenishing podocytes [6, 7]. It was already known that PECs proliferate throughout life at a low rate [8]. PECs are within the same compartment as podocytes. Romagnani and co-workers showed in human kidneys that PECs express proteins, which are also expressed on stem or progenitor cells in other tissues, such as CD133 or CD24. [7] Importantly, a graded expression of progenitor markers was observed to be decreasing towards the differentiated podocytes, whereas podocyte marker expression increased in a reciprocal fashion. This indicated progressive differentiation of the PEC progenitor towards podocytes. In vitro, PEC progenitors could be differentiated into different lineages (e.g. neurons), whereas the ‘committed podocyte progenitors’ could only be differentiated into podocytes. PEC progenitors alleviated adriamycine nephropathy when injected into experimental mice, although it was not clear whether this was due to paracrine effects or the result of engraftment to replenish podocytes [7]. Our group showed in a cell fate tracking experiment in transgenic mice that when irreversibly labelling the cells on Bowman’s capsule shortly after birth, these labelled cells are recruited onto the glomerular tuft during adolescence where they form fully differentiated podocytes [6]. At that time, these results were interpreted to mean that PECs serve to replenish podocytes late in renal development (Figure 1A).

Recently published work, however, questions the hypothesis that PECs may function as progenitors. In the first study from the group of Miyazaki published in this issue [9], putative podocyte progenitors were metabolically labelled by the thymidine analogue BrdU in transgenic NEP25 mice. NEP25 mice express human CD25 under the control of the nephrin promoter in podocytes. Injection of the ligand of hCD25 fused to a toxin (LMB2) allows graded ablation of podocytes, resulting in induction of glomerulosclerosis in ∼20% of all glomeruli in the present study [1]. BrdU was administered continuously during the experiment for 2–4 weeks to metabolically label all proliferating cell populations—including a presumptive progenitor population for podocytes. No BrdU-labelled podocytes could be detected 4 weeks after induction of glomerulosclerosis. Specifically, out of 876 BrdU-positive
nuclei within the glomerular tuft, only 2 were positive for the podocyte marker WT1. These two nuclei were localized within the same cell, indicating mitosis of the nucleus without subsequent cytokinesis, as described previously for podocytes. This study has some limitations. First, the authors assumed that cellular proliferation (and BrdU labelling) must occur within the putative progenitor population during the experiment, which is likely necessary for self-renewal of the presumptive progenitors. Furthermore, the authors localized BrdU-labelled nuclei to podocytes on serial sections and not in double or triple immunostainings. Nevertheless, since the results of this study were so clear it provides a strong argument against the existence of a progenitor population for podocytes.

Two more recent studies address the same question. Wanner et al. [10] explored the existence of a podocyte progenitor population by irreversibly labelling podocytes. In a transgenic model of glomerulosclerosis, they observed a loss of the genetic labelling in ∼5% of all podocytes. This ‘dilution’ of genetically labelled podocytes indicated recruitment of new unlabelled podocytes from an external non-podocyte source. To test whether regenerated podocytes originated from parietal epithelial cells, PECs were genetically labelled and traced in ageing healthy mice as well as in compensatory hypertrophy after unilateral nephrectomy. No significant podocyte recruitment from PECs was observed. One limitation of this study was that podocyte numbers were determined in glomerular single cell preparations using fluorescence-activated cell analysis, which may be susceptible to even minor shifts in fluorescence intensities as a consequence of pathological processes within the experimental tissues. Thus, Wanner et al. detected a relatively small podocyte renewal from an unknown source outside the PEC compartment, which was not sufficient to prevent the formation of glomerulosclerosis. Currently, the most promising candidate progenitors for this purpose are probably the recently proposed renin-producing cells of the macula densa [11].

A second study from our group, published back-to-back with Wanner et al., Berger et al. [12] ruled out recruitment of podocytes from PECs in ageing mice and after progressive renal ablation in adult mice using conventional (labour-intensive) histological techniques. In addition, Berger et al. investigated in more detail the above-described recruitment of fully differentiated podocytes from the PEC compartment in newborn mice [6], which was also confirmed by Wanner et al. [10]. Berger et al. could show that cells on Bowman’s capsule were not only directly labelled by the PEC-specific transgenic mouse (PEC-rTTA) but also by the podocyte-specific mouse (Pod-rTTA). In addition, labelled cells on Bowman’s capsule expressed synaptopodin and higher levels of WT1 than normally found in PECs.
In mice as well as in humans, these synaptopodin-positive cells disappeared from Bowman’s capsule as the glomeruli gradually underwent physiological hypertrophy as a human child grows from 3 to 70 kg in body size. Therefore, a functional ‘podocyte reserve’ directly differentiates into podocytes on Bowman’s capsule probably because sufficient numbers of podocytes can not be accommodated on the relatively small glomerular tuft in the capillary loop stage of glomerular development. These additional podocytes are recruited onto the glomerular tuft during adolescence and contribute to ∼2–10% of the final podocyte pool [6, 12] (Figure 1B).

In summary, PECs were once very good candidates to function as a progenitor population for podocytes, and multiple earlier studies provided data supporting this concept. These studies analysed primarily the expression of marker proteins, in vitro differentiation techniques or injection of cultured cells into animal models. Recent studies, however, consistently argue against PECs as a potential progenitor population for podocytes using in vivo cell tracking methodologies. Instead, a podocyte reserve has been identified on Bowman’s capsule to provide sufficient numbers of podocytes for the impressive physiological glomerular hypertrophy during adolescence. The average body size of mankind has continuously increased with improving health and nutrition since ∼250 years (average height used to be ∼15 cm smaller). It can be speculated that our podocyte endowment may no longer be sufficient to handle the increase in body size (especially in males). This is suggestive for a novel disease of civilization: increased body height and consequent relative podocytopenia as a risk factor for FSGS.

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CONFLICT OF INTEREST STATEMENT

None of the authors declare any financial or intellectual conflict of interest. In particular, results presented in this paper have not been published previously in whole or part, except in abstract format.

(See related article by Miyazaki et al. Mice are unable to endogenously regenerate podocytes during the repair of immunotoxin-induced glomerular injury. Nephrol Dial Transplant 2014; 29: 1005–1012.)

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